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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/776,311
Filing Date: February 11, 2004
Appellant(s): KINNEY ET AL.

Lynne M. Christenbury
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10 February 2009 and supplemented 20 March 2009 appealing from the Office action mailed 16 July 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 1, 12, 16 and 26 under 35 USC 112, first paragraph, as not being supported by an enabling disclosure, has been WITHDRAWN in view of Appellant's arguments provided in the Brief of 10 February 2009.

(7) Claims Appendix

A substantially correct copy of appealed claims 1, 12, 16 and 26 appears on page 14 of the Appendix to the appellant's brief. The minor errors are as follows:

Claim 16, line 2, should have ---or 12--- inserted after "1". The deletion of the phrase "or 12" was proposed in the non-entered After Final amendment of 10 October 2008.

(8) Evidence Relied Upon

6,075,183	KNUTZON ET AL	6-2000
7,211,656	MUKERJI ET AL	5-2007
6,884,921	BROWSE ET AL	4-2005
WO 02/08401	ABBOTT LABORATORIES	1-2002

Abbadi, A. et al. "Biosynthesis of Very-Long-Chain Polyunsaturated Fatty Acids in Transgenic Oilseeds: Constraints on Their Accumulation" The Plant Cell, vol. 16 (October 2004), pp. 2734-2748.

Qi, B. et al. "Production of Very Long Chain Polyunsaturated Omega-3 and Omega-6 Fatty Acids in Plants" Nature Biotechnology, vol. 22, no. 6 (June 2004), pp. 739-745.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 12, 16 and 26 on appeal are rejected under 35 U.S.C. 103(a) as being unpatentable over KNUTZON et al (US 6,075,183) in view of ABBOTT LABORATORIES (WO 02/08401 effectively filed July 2000), further in view of each of MUKERJI et al (US 7,211,656 effectively filed January 2002) or BROWSE et al (US 6,884,921 effectively filed February 1997).

The claims are broadly drawn to a transgenic oilseed plant including Brassica (canola) plants, which produce seeds which contain oil comprising at least 1% of at least one omega-3 polyunsaturated fatty acid (PUFA), wherein said PUFA has at least 20 carbon atoms and at least five carbon-carbon double bonds, wherein the PUFA includes eicosapentaenoic acid (EPA), wherein the plant and seeds comprise transgenes encoding at least one desaturase and at least one elongase.

Knutzon et al teach the various enzymatic pathways for producing PUFAs with at least 20 carbon atoms and at least five carbon-carbon double bonds, wherein untransformed plants are only able to produce polyunsaturated fatty acids with 18 carbons, such as linoleic acid (2 double bonds) and linolenic acid (3 double bonds). Knutzon et al teach that a combination of elongase, delta 6 desaturase, delta 5 desaturase and delta 4 desaturase are required to convert linoleic acid to gamma linolenic acid, which is ultimately converted into the omega-6 PUFA of docosapentaenoic acid (DPA), via a dihomogamma linolenic acid (DGLA) precursor.

Knutzon et al also teach that PUFAs such as DPA are precursors for compounds like prostaglandins which are essential for human health and development, wherein transgenic plants producing PUFAs in their seed oil are useful for nutritional supplements or pharmaceutical compositions. Knutzon et al teach Brassica plant transformation with genes encoding enzymes including delta 5 and delta 6 desaturases operably linked to a seed-specific napin promoter. Knutzon et al teach that said transgenic Brassica plants produced seeds with oil comprising over 11% of new fatty acids including the DGLA precursor.

Knutzon et al also teach that EPA is produced from arachidonic acid (ARA) by a delta-17 desaturase, wherein ARA is produced by subjecting linoleic acid to the combined action of elongase and delta-6 and delta 5 desaturases, and wherein omega-3 PUFAs such as EPA also have beneficial pharmaceutical and nutritional applications (see, e.g., Figure 2; column 1, lines 13-15 and 25-27; column 3, lines 17-18).

Knutzon et al suggest plant transformation with a combination of desaturase and elongase transgenes for the production in plants of PUFAs with at least 20 carbons and at least 5 carbon-carbon double bonds. See, e.g., Figures 1-2; column 1 through column 2, line 45; column 3, lines 1-19; column 4, line 55 through column 5, line 12; column 19, line 27 through column 26.

Knutzon et al do not teach transgenic plants producing at least 1% omega-3 PUFAs with at least 20 carbons and at least 5 double bonds, such as EPA, in their seed oil.

ABBOTT LABORATORIES teaches the desirability of PUFAs including omega-6 DPA for pharmaceutical or nutritional compositions. ABBOTT LABORATORIES teaches the isolation of elongase genes necessary for the production of polyunsaturated 20-carbon fatty acids in plants. ABBOTT LABORATORIES **suggests** plant transformation, including Brassica transformation, with said elongase gene under the control of a seed-specific promoter, for the production of said PUFAs in seed oils. ABBOTT LABORATORIES also teaches that co-transformation with a gene encoding a delta 4 desaturase would also be needed for the production of omega-6 DPA.

See, e.g., Abstract; Figure 1; page 1, bottom paragraph; page 2, top and bottom paragraphs; page 5, lines 15-23; page 6, lines 1-6; page 7, lines 1-6 and 24-31; pages 8-9; page 11, lines 6-13 and 24-31; page 12, line 17 through page 13; page 53, lines 21-27; page 54, line 15 through page 55, line 18.

ABBOTT LABORATORIES also teaches the advantages of EPA as a nutritional and pharmaceutical component, and that the combination of elongase and delta-5 elongase is required for EPA production. ABBOTT LABORATORIES also **suggests** the use of a transgene encoding another desaturase, including a delta-17 desaturase (see, e.g., page 1, lines 22-24; page 8, lines 15-18; page 13, lines 4-7; page 55, lines 3-5 and 10-12).

Mukerji et al teach that omega-3 desaturase and delta-17 desaturase are synonyms, and that this enzyme is required for the production of EPA, which has nutritional and pharmaceutical applications. Mukerji et al teach that yeast transformed with an isolated gene encoding this enzyme and a delta-5 desaturase gene produced

EPA. Mukerji et al also teach that yeast transformed with this gene alone produced EPA when exposed to a precursor. Mukerji et al **suggest** oilseed transformation, including Brassica transformation, with a seed-specific promoter operably linked to said transgenic coding sequences, for the production of EPA in transgenic seed oil.

See, e.g., Figures 1- 2; columns 1-4; column 5, lines 45-49; column 6, lines 8-37; column 7, lines 1-5; column 15, lines 41-48; column 16, lines 1-20 and 60-66; column 32, lines 5-44; column 33, lines 1-40; column 35, line 24 through column 37, line 12.

Browse et al teach the isolation of a gene encoding an omega-3 desaturase enzyme, which desaturates ARA to EPA by introducing a double bond at carbon position 17. Browse et al teach that transgenic plants comprising said transgene produced high levels of EPA when sprayed with the ARA precursor substrate. Browse et al teach that EPA is useful as a nutritional or pharmaceutical supplement. Browse et al **suggest** Brassica plant transformation with the desaturase gene under the control of a seed-specific promoter.

See, e.g., Figure 1; column 1, lines 24-42; column 2, lines 13-22; column 3, lines 13-45; column 7, lines 6-20; column 12, lines 15-25 and 45-49; column 15, lines 18-21; column 16, lines 46-67; column 17, lines 26-30 and 41-60; column 18, lines 26-30 and 40-67; column 19, lines 1-10; column 20, lines 9-20; claims 1-4 and 6-15.

It would have been obvious to one of ordinary skill in the art to utilize the method of Brassica transformation with the delta 5- and delta 6- desaturase genes, under the control of the seed-specific napin promoter, for the production of novel PUFAs in the seed oil of transgenic plants as taught by Knutzon et al; and to modify that

method by incorporating the elongase genes taught by ABBOTT LABORATORIES under the control of a seed-specific promoter; given the suggestion to do so by Knutzon et al and ABBOTT LABORATORIES.

It would have been further obvious to further modify that method by incorporating the omega 3/delta 17 desaturase genes taught by each of Mukherji et al or Browse et al, under the control of a seed-specific promoter such as the napin promoter, for the production of EPA in the oil of the transgenic Brassica seeds; as suggested by each reference.

Given the high levels of novel PUFA produced by the transgenic organisms taught by each of Knutzon et al, Mukherji et al or Browse et al, **one of ordinary skill in the art would have reasonably expected** the instantly claimed levels of EPA in the seed oil; as influenced by the highly expressed seed-specific napin promoter and the high proportion of oil in Brassica seeds.

(10) Response to Argument

Appellant's Arguments

I. Appellant urges that the production of EPA or DHA in plant seed oil, when utilizing the transgenes taught by the cited combination of references, was *unexpected* at the time of the invention; given the belief at the time of the invention that an *acyltransferase gene* was needed to transport the fatty acid substrates to and from the cell membrane, in order to facilitate the combined action of the desaturase and the elongase enzymes which were localized in different cellular components. See, e.g.,

page 10 of the Brief of 10 February 2009 (hereinafter "Brief"), bottom three paragraphs. Appellant cites Robert et al (2006), a Review article, and Wu et al (2005), to support this position. See, e.g., page 11 of the Brief, top three paragraphs. These references were first cited to support this position in the Response of 17 April 2008.

The Examiner disagrees with Appellant's characterization of the state of the art at the time of their invention. The Examiner maintains that two other research groups concurrently executed plant transformation experiments to produce PUFAs, and that neither group selected an acyltransferase gene as part of their strategy. Specifically, the Examiner relies upon Abbadi et al (2004, mentioned in the telephonic interview of 16 April 2008, and cited by Robert et al on page 105, paragraph bridging the columns), and Qi et al (cited in Robert et al as being the first published demonstration of EPA production in transformed plants; see, e.g., page 104 of Robert et al, column 1, bottom paragraph).

The Examiner's discussion of Abbadi et al and Qi et al, in this context, was previously presented in the Office action mailed 16 July 2008, in response to Appellant's allegations at the time. Abbadi et al was submitted by the prior examiner with the Office action of 08 August 2006. It appears as the fourth NPL reference above the 892 entry in the Image File Wrapper. Qi et al was submitted with the Office action of 16 July 2008.

The Examiner notes that Appellant's PCT application, corresponding to the instant application, was published on 26 August 2004. Appellant's allege that they were the *first* research group to publicly disclose the claimed invention, wherein they were

also the *first* to publicly disclose that an *acyltransferase gene was not required* to obtain the claimed levels of the claimed PUFAs. The Examiner respectfully disagrees.

Qi et al (June 2004) demonstrate high levels of EPA production in transgenic plants, when transformed with a combination of two desaturase genes and one elongase gene; namely a delta-9 elongase, a delta-8 desaturase from the same pathway, and a delta-5 desaturase gene (see, e.g., page 740; page 741, Table 1 and column 1). Qi et al obtained 3% EPA in the leaves of transgenic plants, since they utilized a constitutive promoter (see, e.g., Table 1). *No acyltransferase transgene* was utilized or reported.

Thus, *the earliest report* of EPA production in transformed plants *did not lead* the artisan of ordinary skill to expect failure, in the absence of a heterologous acyltransferase gene. Moreover, Qi et al suggested the use of a seed-specific promoter to obtain high levels of EPA in the seed oil (see, e.g., page 743, column 2, penultimate paragraph), which promoter type was taught by the references cited by the Examiner.

Given the *high levels* of EPA produced in the leaves of *transformed plants* obtained by Qi et al, when using a constitutive promoter, which is generally expressed throughout the plant; one of ordinary skill in the art would have *reasonably expected* equally high levels of EPA produced *in the seed*, when a *seed-specific promoter* was utilized, as suggested by Qi et al.

Regarding Appellant's discussion of transport across the cell membrane and within various intracellular organelles, the Examiner is not aware of any differences between the membranes and organelles of individual leaf cells versus those in

individual seed cells. Thus, one of ordinary skill in the art would have expected successful EPA production in the seed at the claimed levels, given the success and suggestions of Qi et al.

Abbadi et al (October 2004) utilized two desaturase genes, a delta-5 and delta-6 desaturase, and one delta-6 elongase gene, under the control of seed-specific promoters, for the production of up to 1% EPA in transgenic flax seeds (see, e.g., page 2735, Figure 1 and paragraph bridging the columns; page 2736, Figure 2; page 2738, Table 1), which is commensurate with the instantly claimed EPA levels. Abbadi et al later suggest the use of an acyltransferase gene as *one of several* options for obtaining *even higher* EPA levels (see, e.g., page 2745, column 1, first full paragraph, where *another* option is suggested).

Abbadi et al was published only two months after the publication of Appellant's PCT application in August 2004. It is unlikely that Abbadi et al conceived and executed their experiments solely on the basis of Appellant's PCT disclosure, within these two months. See in particular page 2747 of Abbadi et al, first column, directly under Acknowledgments, where it is disclosed that Abbadi et al submitted their publication in July 2004, one month prior to Appellant's PCT publication date.

The Examiner maintains that Abbadi et al's *suggestion* of *various* additional genes *does not demonstrate* the belief by the artisan of ordinary skill that the acyltransferase gene was absolutely essential for any EPA production. Furthermore, it is noted that Abbadi et al's suggestion of incorporating additional genes was merely made *in order to optimize and increase the already substantial* levels of EPA produced

in their transgenic seeds. Even *without* these suggested additional genes, Abbadi et al teach the production of EPA in transgenic seeds *at levels encompassed by the instant claims*.

Appellant urges that the Examiner's reliance upon Qi et al and Abbadi et al is improper, since Appellant's PCT application has an effective filing date of February 2003, based upon a provisional US application, which predates the above two publications (see, e.g., page 9 of the Brief, bottom two paragraphs).

The Examiner maintains that Qi et al and Abbadi et al were cited *to demonstrate the state of the art* at the time of Appellant's *published* PCT application. Even though Appellant *conceived* their invention prior to the publication of either Qi et al or Abbadi et al, they did not *publish* their invention until *after* the publication of Qi et al or the submission of Abbadi et al, and *within two months* of the publication of Abbadi et al. The Examiner is *not* relying upon these references *as prior art* against Appellant's claims, for the reasons presented by Appellant.

II. Appellant urges that *none* of the cited prior art references *singly teach* the claimed levels of EPA in transgenic oilseeds, and that there was *no motivation to combine* the teachings of the cited references (see, e.g., page 11 of the Brief, bottom three paragraphs, through page 12).

The Examiner maintains that **Knutzon** et al teach that Brassica plants transformed with heterologous desaturase genes produced seeds which had oil comprising over 11% of new fatty acids. See, in particular Tables 4 and 5 of Knutzon et

al, columns 21-26, depicting Brassica transformation with either a delta-5 desaturase gene (Table 4) or a delta-6 desaturase gene (Table 5).

Seed oil in delta-5 transformed plants produced 4-6% of the novel (5,9)18:2 fatty acid, the corresponding end-product of the reaction catalyzed by this enzyme on endogenous substrates; as opposed to 0% for the untransformed control in the top row of Table 4. Seed oil in delta-6 transformed plants produced up to 4.94% of the novel (6,9)18:2 fatty acid, and over 15% of the novel 18:3ga fatty acid; as opposed to 0% of these fatty acids in the seed oil of untransformed control plants, as depicted in the top 10 rows of Table 5.

Moreover, Knutzon et al teach that over 1% ARA was produced in transgenic leaves (see, e.g., column 21, lines 35-37), wherein ARA is a 20 carbon and 4 double bond precursor to EPA, one of the claimed PUFAs.

Thus, Knutzon et al teach the production of high levels of novel fatty acids in leaves and seeds, following transformation with desaturase genes; and also suggest the incorporation of elongase genes, as discussed above.

Given *these high levels* of novel fatty acid production, one of ordinary skill in the art *would have recognized that high levels of EPA* would be obtained following the addition of elongase genes taught by ABBOTT LABORATORIES, and following the addition of the delta-17/omega-3 desaturase gene taught by each of Mukerji et al and Browse et al; in order to produce high levels of each substrate and intermediate required for PUFA production; as suggested by each of the references.

Regarding the *motivation to combine* references, the Examiner maintains that each reference contains strong suggestions to combine the various transgenes necessary to obtain the claimed invention, as discussed above.

Moreover, Robert et al (2006), cited as Appendix D by Appellant, *attribute the instant inventors' success*, and *the success of Wu et al* (2005, Appellant's Appendix F), to the use of a transgene encoding a *delta-17 desaturase*, which converts omega-6 fatty acids into omega-3 fatty acids (see, e.g., page 106, column 1, first two full paragraphs). However, it is noted that the *instantly appealed* claims *do not* recite a delta-17 desaturase gene.

See In re Lindner, 173 USPQ 356 (CCPA 1972) and In re Grasselli, 218 USPQ 769 (Fed. Cir. 1983) which teach that the evidence of nonobviousness should be commensurate with the scope of the claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Conclusion

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/David T Fox/

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15 June 2009